

Appl. No. : 10/735,418
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AMENDMENTS TO THE CLAIMS

1. **(Withdrawn)** A compound which binds to Bcl-2 and modulates the activity of Bcl-2 in a cell so as to be inductive of apoptosis, and wherein the compound does not cleave Bcl-2.
2. **(Withdrawn)** The compound of Claim 1 wherein said compound induces a conformational change in Bcl-2.
3. **(Withdrawn)** The compound of Claim 1 wherein said compound is selected from the group consisting of a peptide, peptidomimetic, an antibody or part thereof and a small organic molecule.
4. **(Withdrawn)** The compound of Claim 1, wherein the compound comprises TR3.
5. **(Withdrawn)** The compound of Claim 1, wherein the compound comprises the DC1 region of TR3.
6. **(Withdrawn)** A compound which binds to Bcl-XL and modulates the activity of Bcl-XL in a cell so as to be inductive of apoptosis, and wherein the compound does not cleave Bcl-XL.
7. **(Withdrawn)** The compound of Claim 5 wherein said compound is selected from the group consisting of a peptide, peptidomimetic, an antibody or part thereof and a small organic molecule.
8. **(Withdrawn)** The compound of Claim 5 wherein the compound comprises TCTP.
9. **(Withdrawn)** The compound of Claim 5 wherein the compound comprises a peptidomimetic mimicking TCTP.
10. **(Withdrawn)** A method of inducing apoptosis in a mammalian cell, comprising contacting said cell with an effective amount of a compound which binds to Bcl-2 and modulates the activity of Bcl-2 in said cell so as to be inductive of apoptosis.
11. **(Withdrawn)** A method of inducing apoptosis in a mammalian cell, comprising contacting said cell with an effective amount of a compound which binds to Bcl-XL and modulates the activity of Bcl-XL in said cell so as to be inductive of apoptosis.
12. **(Withdrawn)** A method of inhibiting apoptosis in a mammalian cell, comprising contacting said cell with an effective amount of a compound that prevents the binding of TR3 and Bcl-2.

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13. **(Withdrawn)** The method of Claim 11, wherein said compound comprises a peptide, peptide analogue, or small molecule designed to block association between TR3 and Bcl-2.

14. **(Withdrawn)** A method of inhibiting apoptosis in a mammalian cell, comprising contacting said cell with an effective amount of a compound that prevents the binding of TCTP and Bcl-XL.

15. **(Withdrawn)** The method of Claim 13, wherein said compound is selected from the group consisting of: a peptide, a peptide analogue, an antibody or part thereof and a small molecule designed to block association between TCTP and Bcl-XL.

16. **(Withdrawn)** The method of Claim 13, wherein said compound comprises TCTP antisense RNA.

17. **(Withdrawn)** A method of identifying molecules that inhibit apoptosis, comprising measuring the amount of labeled TCTP or TR3 bound to Bcl-2 family proteins anchored to a solid support in the presence and absence of molecules being tested, and determining the ability of each said molecule being tested to compete with TCTP or TR3 for binding sites on Bcl-2 family proteins.

18. **(Currently Amended)** A method of identifying molecules that induce apoptosis, comprising:

determining the ability of said molecule to bind to the loop region of a Bcl-2-family protein and modulate the activity of said protein so as to be inductive of apoptosis.

19. **(Currently Amended)** A method of identifying molecules that induce apoptosis, comprising screening compounds using ~~NMR~~ for binding to ~~N15-Bcl-2~~ isotope-labeled Bcl-2 at the same site where TR3 binds, said site being different from the BH3-binding site on Bcl-2, said screening comprising:

interacting isotope-labeled Bcl-2 with said compound in an appropriate buffer system to form a complex; and

identifying where the compound is binding.

20. **(Withdrawn)** The method of Claim 17, additionally comprising ¹³C labeling of Bcl-2.

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21. **(Currently Amended)** A method of identifying molecules that induce apoptosis, comprising:

screening compounds ~~using NMR for binding to~~ determine whether they bind to N15-Bcl-XL Bcl-XL labeled with an isotope at the same site where translationally controlled tumor protein (TCTP) binds, said site being different from the BH3-binding site on Bcl-XL, and
assaying any of said compounds which bind to Bcl-XL labeled with an isotope at the same site where TCTP binds to determine whether the compound induces apoptosis.

22. **(Withdrawn)** The method of Claim 17, additionally comprising ¹³C labeling of Bcl-XL.

23. **(Currently Amended)** A method for identifying molecules that induce apoptosis, comprising:

(a) ~~detecting~~ providing a labeled Bcl-2 binding compound bound to Bcl-2 forming a complex, wherein said Bcl-2 binding compound is known to induce a conformational change in Bcl-2 so as to be inductive of apoptosis;

(b) contacting the Bcl-2 binding compound – Bcl-2 complex with a candidate agent, the candidate agent suspected of being able to induce a conformational change in Bcl-2 so as to be inductive of apoptosis, and

(c) detecting dissociation of the labeled Bcl-2 binding compound from the complex, ~~whereby the candidate compound is identified as an agent that induces apoptosis, and~~

(d) assaying the candidate agent to determine whether the candidate agent induces apoptosis.

24. **(Currently Amended)** The method of claim ~~24~~23 wherein said Bcl-2 binding compound is selected from the group consisting of: TR3, the ligand binding domain of TR3, an antibody that mimics TR3, a peptide comprising the DC1 region of TR3, a functional fragment of TR3, and a peptidomimetic, wherein said Bcl-2 binding compound binds to Bcl-2 and modulates the activity of Bcl-2 in a cell so as to be inductive of apoptosis.

25. **(Currently Amended)** The method of claim ~~24~~23 wherein the said Bcl-2 protein is a fragment of the Bcl-2 protein comprising the BH3 and BH4 domains.

26. **(Currently Amended)** The method of claim ~~24~~23 wherein the said Bcl-2 protein is a fragment of the Bcl-2 protein comprising the N-terminal loop region, located between the BH4 and BH3 domains.

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27. **(Currently Amended)** The method of claim 21 wherein ~~the method is carried out using SAR~~ by NMR is used to identify a structure-activity relationship (SAR) between said Bcl-2 and said candidate agent.

28. **(Currently Amended)** The method of claim 21 wherein ~~the method~~ said screening is carried out using high throughput screening.

29. **(Currently Amended)** A method for identifying molecules that induce apoptosis, comprising:

(a) detecting a labeled Bcl-X_L binding compound bound to Bcl-X_L, wherein said Bcl-X_L binding compound is known to induce a conformational change in Bcl-X_L so as to be inductive of apoptosis;

(b) contacting the Bcl-X_L binding compound – Bcl-X_L complex with a candidate agent, the candidate agent suspected of being able to induce a conformational change in Bcl-X_L so as to be inductive of apoptosis, and

(c) detecting dissociation of the labeled Bcl-X_L binding compound from the complex, and

(d) assaying the candidate agent to determine whether ~~whereby~~ the candidate agent ~~compound~~ is ~~identified as an agent that induces apoptosis.~~

30. **(Currently Amended)** The method of claim 21 wherein said Bcl-X_L binding compound is selected from the group consisting of: translationally controlled tumor-associated protein (TCTP) or a functional fragment thereof, an antibody which mimics the action of TCTP, and a peptidomimetic, wherein said Bcl-X_L binding compound binds to Bcl-X_L and modulates the activity of Bcl-X_L in a cell so as to be inductive of apoptosis.

31. **(Currently Amended)** A method for identifying molecules that induce apoptosis, comprising:

(a) contacting Bcl-2 with a candidate compound in the presence of a multidomain pro-apoptotic Bcl-2-family protein, and

(b) detecting the association of Bcl-2 with such multidomain pro-apoptotic Bcl-2-family protein, whereby if association occurs, the candidate compound is identified as an agent that induces apoptosis.

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32. **(Currently Amended)** A method for identifying molecules that induce apoptosis, comprising:

(a) contacting Bcl-X_L with a candidate compound in the presence of a multidomain pro-apoptotic Bcl-2-family protein, and
(b) detecting the association of Bcl-X_L with such multidomain pro-apoptotic Bcl-2-family protein, whereby if association occurs, the candidate compound is identified as an agent that induces apoptosis.

33. **(Currently Amended)** A method for identifying molecules that induce apoptosis, comprising:

(a) contacting Bcl-2 with a candidate compound and a BH3 specific antibody under conditions where the BH3 domain of Bcl-2 is not accessible to a BH3 specific antibody, and
(b) detecting the association of the BH3 specific antibody to the BH3 domain of Bcl-2, whereby if association occurs the candidate compound is identified as an agent that induces apoptosis.

34. **(Withdrawn)** A method of inducing apoptosis in a cell comprising administering a compound capable of inducing a conformational change in Bcl-2 so as to be inductive of apoptosis.

35. **(Withdrawn)** The method of claim 32 wherein the compound works through inducing TR3 to localize to the mitochondria of the cell.

36. **(Withdrawn)** A method of inducing apoptosis in a mammalian cell, comprising contacting said cell with an effective amount of a compound which enhances the binding of TR3 to Bcl-2 in said cell so as to be inductive of apoptosis.

37. **(Withdrawn)** An antibody specific for the BH3 domain of Bcl-2 which can be used to determine whether Bcl-2 has undergone a conformational change so as to be inductive of apoptosis.

38. **(NEW)** The method of Claim 18, wherein said determining is by measuring the amount of labeled translationally controlled tumor-associated protein (TCTP) or TR3 bound to Bcl-2 family proteins anchored to a solid support in the presence and absence of molecules being tested, and determining the ability of each said molecules being tested to compete with TCTP or TR3 for binding sites on Bcl-2 family proteins.

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39. **(NEW)** A method of identifying molecules that induce apoptosis, comprising:
screening compounds using NMR for binding to isotope-labeled Bcl-XL at the same site where TCTP binds, said site being different from the BH3-binding site on Bcl-XL, comprising:

interacting isotope-labeled Bcl-XL with said compound in an appropriate buffer system; and

performing NMR on said complex to identify where the compound is binding, whereby when said candidate compound binds at the same site where TCTP binds, which is different from the BH3-binding site on Bcl-XL, the candidate compound is identified as an agent that induces apoptosis.

40. **(NEW)** The method of claim 39, wherein said isotope is selected from the group consisting of ^{15}N , ^{13}C , and ^2H .

41. **(NEW)** The method of Claim 39, wherein said isotope is ^{15}N .

42. **(NEW)** The method of Claim 19, wherein said isotope is selected from the group consisting of ^{15}N , ^{13}C , and ^2H .

43. **(NEW)** The method of Claim 19, wherein nuclear magnetic resonance (NMR) is used to identify where the compound is binding.

44. **(NEW)** The method of Claim 21, wherein said isotope is selected from the group consisting of ^{15}N , ^{13}C , and ^2H .

45. **(NEW)** The method of Claim 21, wherein nuclear magnetic resonance (NMR) is used to identify where the compound is binding.